REMARKS/ARGUMENTS

I. Change of Attorney Docket No.:

At the outset, Applicants would like to inform the Examiner that the Attorney Docket No. for the instant application has changed.

The new Attorney Docket No. for the instant application is **36119.156US3**.

II. Amendments to the Specification:

The specification has been amended to correct several clerical/typographical errors. No new matter has been added by way of these amendments to the specification.

III. Amendments to the Claims:

Claims 1-11 and 25 were under consideration. Claims 12-24 were withdrawn pursuant to 37 C.F.R. § 1.142(b). Applicants note that the Examiner has indicated that when the claims drawn to the product are allowable, the process claims (claims 12-24) would be rejoined (*see*, Office Action, page 2, first paragraph).

Claims 1-11 and 25 have been cancelled without prejudice or disclaimer of the subject matter contained therein. These claims have been cancelled for reasons unrelated to patentability. Applicants reserve the right to pursue the subject matter of the cancelled claims in this or a future related application.

Claims 26-40 have been newly added. Support for the newly added claims can be found throughout the specification as originally filed. It is submitted that no new matter has been added by way of the instant amendment to the claims.

IV. Withdrawl of Prior Objections/Rejections:

Applicants gratefully acknowledge that the rejection of claims 1-11 and 25 under 35 U.S.C. § 103(a) as being unpatentable over Harnish *et al.* (*J. Biol. Chem.* **273**:9270-9278, 1998) and Ameis *et al.* (*J. Biol. Chem.* **265**:6552-6555, 1990) in view of Norris *et al.* (*J. Biol. Chem.* **270**:22777-22782, 1995), USPN 5,908,859, or Dichek *et al.* (*J. Biol. Chem.* **273**:1896-1903, 1998), and further in view of Kwok *et al.* (*Nature* **270**:177-178, 1994) has been withdrawn (*see*, Office Action, paragraph bridging pages 2-3).

V. Rejection under 35 U.S.C. § 103(a):

The Office Action rejected claims 1-11 and 25 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Harnish *et al.* (*J. Biol. Chem.* **273**:9270-9278, 1998) and Ameis *et al.* (*J. Biol. Chem.* **265**:6552-6555, 1990) in view of either Landschultz *et al.* (*Science* **243**:1681-1688, 1989) or Birkenmeier *et al.* (*Genes Dev.* **3**:1146-1156, 1989), and further in view of Norris *et al.* (*J. Biol. Chem.* **270**:22777-22782, 1995), USPN 5,908,859, or Dichek *et al.* (*J. Biol. Chem.* **273**:1896-1903, 1998) (*see,* Office Action, page 3).

According to the Office Action, the primary references (*i.e.,* Harnish *et al.* and Ameis *et al.*) allegedly teach all the materials and/or technology necessary to make and use a transformed cell. Specifically, the Office Action relies on Ameis *et al.* to teach a human hepatic lipase (HL) promoter/enhancer, and Harnish *et al.* to teach a DNA construct expressing an estrogen receptor (ER), and an apoAI promoter/enhancer reporter construct (*see,* Office Action, page 4).

The Office Action further cites either of the secondary references (*i.e.,* Landschultz *et al.* or Birkenmeier *et al.)* purportedly to teach how to make a vector encoding a C/EBP transcription factor (*see,* Office Action, pages 4-5).

The Examiner admits that none of the primary or secondary references teach one of ordinary skill in the art why they should introduce the three nucleic acid molecules (*i.e.,* ER, C/EBP and HL reporter) into a cell as recited in Applicants' claims (*see,* Office Action, page 5, second paragraph). For this motivation to introduce the three nucleic acid molecules into a cell, the Examiner relies on any of the tertiary references (*i.e.,* Norris *et al.,* USPN 5,908,859 ("the '859 patent"), or Dichek *et al.*). Specifically, the Office Action states that Dichek *et al.* teach both that HL can act as a ligand to remove apoB-containing lipoproteins from plasma, and the relationship between HL and apoAI. The Office Action relies on the '859 patent for teaching the relationship between estrogen and lipid metabolism (*see,* Office Action, page 5, third paragraph).

The Office Action alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make and use the claimed invention with reasonable expectation of success since all of the necessary components of the claimed cells are taught by the prior art (*see,* Office Action, page 5, last paragraph).

Applicants have cancelled claims 1-11 and 25 without prejudice or disclaimer of the subject matter recited therein. Accordingly, this rejection under § 103(a) has been rendered moot. Nonetheless, Applicants will address this prior art rejection in the context of the currently pending claims.

Applicants respectfully assert that the Office Action has failed to establish a *prima facie* case of obviousness for the reasons described below.

The sole independent claim in the instant application, claim 26, recites a cell comprising (i) an exogenous nucleic acid molecule which encodes an estrogen receptor; (ii) an exogenous nucleic acid molecule which encodes a CCAAT/enhancer-binding protein (C/EBP) transcription factor; and (iii) a reporter gene operatively associated with a hepatic lipase (HL) promoter.

It is well settled that in order to establish a *prima facie* case of obviousness under § 103(a), the Examiner must show that some objective teaching, suggestion or motivation in the applied prior art taken as a whole and/or knowledge generally available to one of ordinary skill in this art would have led that person to the claimed invention as a whole, including each and every limitation of the claims, without recourse to the teaching in Applicants' disclosure. *See generally, In re Lee*, 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002); *In re Rouffett*, 149 F.3d 1350, 1358, 47 USPQ2d 1453, 1458 (Fed. Cir. 1998); and *In re Fritch*, 972 F.2d 1260, 1265-66, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992).

The Office Action has not met its burden of providing any objective teaching, suggestion or motivation in the applied prior art taken as a whole, as to why one of ordinary skill in the art would modify the cited references to arrive at Applicants' claimed invention. The Office Action has simply identified the different elements present in Applicants' claimed invention among several references, and alleged that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make and use the claimed invention with reasonable expectation of success since all of the necessary components of the claimed cells are taught by the prior art. That "all of the necessary components of the claimed cells are taught by the prior art" is wholly insufficient grounds to reject Applicants' claims under § 103. There must be a motivation to combine all of these components.

The Federal Circuit has stated that

> identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather, to establish obviousness based on a combination of elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant." *In re Kotzab*, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000).

The Federal Circuit has also made clear that the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine prior art references. An adequate showing of motivation to combine requires "evidence that a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Ecolochem, Inc. v. Southern Calif. Edison Co.*, 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075 (Fed. Cir. 2000). "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

None of the references cited by the Examiner, taken alone or in combination, teach or suggest Applicants' claimed invention. Specifically, none of the references teach, suggest or provide motivation for introducing a C/EBP transcription factor into a cell comprising an exogenous nucleic acid molecule encoding estrogen receptor, and a hepatic lipase reporter construct.

Ameis *et al.* report that the human hepatic lipase gene 5'-nontranscribed region contains multiple cis-elements such as "TATA" box sequences, a hepatocyte-specific factor binding site "AGGTTAATTATTAAT," "Alu" repeat sequences, "CCAAT" elements, a cyclic AMP response element, and a glucocorticoid response element (*see*, page 6555, left column, first full paragraph). As a preliminary matter, one of ordinary skill in the art would readily recognize that short cis-elements like TATA or CCAAT, have a high probability of appearing frequently in a sequence the size of the 5' non-transcribed region of HL, and that most of these occurrences would not correlate with functional activity. It is notable in this

context that neither Ameis *et al.*, nor any of the other Examiner-cited references, test whether any transcription factors bind the reported cis-elements and/or whether any of these cis-elements are functional.

The mere fact that a cis-element with homology or identity to known transcription factor binding sites exists in an upstream non-transcribed region, does not immediately imply that that site is bound by a transcription factor and/or that that site is involved in the functional regulation of the downstream gene. This supposition needs to be established by further experimentation. Even if we assume *arguendo* that all of the cis-elements in the HL promoter/enhancer contribute to the regulation of the HL gene, none of the Examiner-cited references teach or suggest which proteins bind these elements. One of ordinary skill in the art at the time of the filing of the instant application would have been aware that a cis-element can be recognized by more than one transcription factor. For example, CCAAT sites were known to bind proteins, other than C/EBP, such as NF-Y, CTF, CP1, and CDP. Thus, a protein that is distinct from C/EBP may bind the CCAAT elements in the HL 5′ non-transcribed region. In the absence of further detailed promoter/enhancer analysis, one of ordinary skill in the art would have no reason to conclude that C/EBP regulates the HL gene, merely because the 5′ non-transcribed region contains CCAAT elements.

Even if arguendo, C/EBP were shown to bind the HL promoter/enhancer (which it is not), neither Ameis *et al.*, nor any of the Examiner cited references, teach or suggest that estrogen receptor be introduced along with C/EBP to regulate the HL gene. Applicants respectfully assert that one of ordinary skill in the art would have been more inclined to select transcription factors that bind to hepatocyte specific factors (*e.g.*, the factor that binds to AGGTTAATTATTAAT) for introduction with the HL promoter/enhancer than a protein that binds a more general cis-element (*e.g.*, C/EBP), and expect a reasonable measure of success.

Harnish et al., the other primary reference, does not remedy the deficiency of Ameis et al.

Furthermore, the secondary references, Landschultz *et al.* and/or Birkenmeier *et al.*, also do not cure the deficiency of the primary reference, Ameis *et al.* These two references merely teach that C/EBP expression vectors were available at the time of the filing of the

instant application. However, neither of these references, nor for that matter, any of the other Examiner-cited references, teach or suggest that C/EBP regulates the hepatic lipase promoter in combination with estrogen receptor.

The Examiner suggested that the tertiary references provide motivation to combine the three nucleic acid molecules of Applicants' claimed invention into a cell. Applicants can find no teaching, suggestion or motivation in the tertiary references regarding introducing C/EBP into a cell comprising exogenous ER and a HL reporter gene.

Applicants respectfully aver that the Examiner has improperly used Applicants' disclosure as a blueprint for piecing together the prior art to defeat patentability of Applicants' claimed invention.

In summary, because none of the Examiner-cited references provides any teaching, suggestion or motivation to arrive at Applicants' claimed invention, Applicants respectfully contend that this rejection under 35 U.S.C. § 103(a) has been erroneously applied and respectfully request that it be withdrawn.

CONCLUSION

Claims 26-40 are pending in the instant application.

Applicants aver that all grounds of rejection have been overcome. Accordingly, Applicants respectfully request reconsideration and allowance of the claims of the instant application. If the Examiner believes that any further discussion of this communication would be helpful, she is encouraged to contact the undersigned at the phone number listed below.

Applicants petition for a two-month extension of time to respond to the Final Office Action of July 30, 2004. Please charge the requisite amount to our Deposit Account No. 08-0219.

Other than the two-month extension of time and RCE fees, no additional fees are believed to be due in connection with this communication. However, if any additional fees are due, please apply any additional charges, or credit any overpayment, to our Deposit Account No. 08-0219.

Respectfully submitted,

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